SPECIFICITY OF STREPTOCOCCI ISOLATED FROM PATIENTS WITH SKIN DISEASES: STUDIES ON PEMPHIGUS, DERMATITIS HERPETIFORMIS, LUPUS ERYTHEMATOSUS AND ERYTHEMA MULTIFORME[1]

III. Lupus Erythematosus Disseminatus

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An analysis of the evidence that has been accumulated to date suggests that the syndrome of disseminated lupus erythematosus is that of toxemia, probably attributable to an infectious agent. However, no conclusive proof of this theory has been established. The investigations described in this report support the specificity of a streptococcus isolated from patients who had disseminated lupus erythematosus.

REVIEW OF LITERATURE

A comprehensive review of the literature, through 1930, dealing with the etiologic and precipitating factors in this disease has been included in the monograph by F. Veiel (1). After thorough analysis of the available data, he offers the theory that lupus erythematosus is a disease of specific origin having an etiologic unity in which the skin manifestations are caused by the local action of the living agent. In 1931, Madden (2) presented nine cases and in the same year Mook, Weiss and Bromberg (3) reported thirteen cases of lupus erythematosus disseminatus, and reviewed the literature to date. Since these authors have recorded the facts from literature up to 1931, I shall avoid repetition, adding only the significant evidence presented since that date.

The precipitating factors of solar or phototherapeutic irradiation in lupus erythematosus disseminatus have been further emphasized by Goeckerman (4), Brain (5), Roxburgh (6), Bechet (7), O'Leary (8) and others.

After analysis of their reports, one cannot doubt but that both natural and artificial sunlight act as precipitating factors in the development of lupus erythematosus, but no evidence is presented to prove that they are of etiologic significance. On considering the fact that in innumerable cases of sunburn, lupus erythematosus develops in only a very small percentage, it becomes apparent that there must be another and more essential factor in addition to the light which causes the typical disease picture.

The controversy regarding the relationship of tuberculosis to lupus erythematosus disseminatus has been continued. Additional reports regarding the asso-

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ciation of lupus erythematosus with systemic tuberculosis have been made. Bruner and Wasowicz (9) in a study of the lungs in forty-seven cases found no lesions of these organs in thirty-seven, healed tuberculosis in three, tuberculosis with doubtful activity in one, and the presence of tuberculosis in the remainder was doubtful. In no instance was active tuberculosis found. O'Leary (8) reported twenty cases of acute disseminated lupus erythematosus and twenty-seven with subacute disseminated lupus erythematosus. X-ray of the chest in the twenty acute cases showed no tuberculosis in fourteen, healed tuberculosis in five, and active tuberculosis in one. In the twenty-one of the subacute cases examined x-ray of the chest showed no tuberculosis in nineteen, healed tuberculosis in one and thickened pleura at the base of the left lung with calcified lymph nodes in one. Necropsy on ten of the patients who had the acute type of the disease revealed healed tuberculosis in three, active tuberculosis, mesenteric lymphadenitis, enteritis, peritonitis and splenitis in one, and a granuloma of the lungs which might have been tuberculosis in one. In the other five no evidence of tuberculosis was found. Franck (10) reported that only one of his cases had a tuberculous terrain. Rose and Goldberg (11) reported five cases of acute disseminated lupus erythematosus, upon three of which autopsy was performed. No evidence of tuberculosis was found. Lyon (12) reported two fatal cases of acute disseminated lupus erythematosus in which no clinical or autopsy evidence of tuberculosis was found. Roxburgh (6) reported five fatal cases of acute disseminated lupus erythematosus; all of these five patients died of streptococcal septicemia and no evidence of tuberculosis was found in any of them. Weidman and Gilman (13) report a case of acute disseminated lupus erythematosus which followed miscarriage complicated by endocervicitis, arthritis and endocarditis. At necropsy no tuberculosis was found. Streptococci were recovered from the heart valves. These observers believe that acute disseminated lupus erythematosus is of the order of chronic erythema multiforme and not on a tuberculous basis. In contrast to these reports is that of Kren (14) who reported that he found some sign or symptom of tuberculosis in all of sixty-six cases having either discoid or disseminated lupus erythematosus. Of extreme significance in this regard is the critical review based on observations at necropsy by Keil (15). Of the 125 cases of lupus erythematosus studied, 20 per cent showed evidence of active tuberculosis. In twenty-six cases inactive tuberculosis was found. In more than 50 per cent of these cases no evidence of tuberculosis in any form was found. For comparison, twenty-six cases of impetigo herpetiformis were studied and here also 20 per cent were found to have active tuberculosis. Keil concluded that the occurrence of tuberculosis in acute disseminated lupus erythematosus is coincidental and unrelated to the lupus erythematosus.

Medullary and caseous lesions in patients with disseminated lupus erythematosus have been reported by Schaumann (16). He states that in the x-ray film these lesions appear as clear or vesicle-like spots, not the classic lesions of tuberculosis. From observations in four cases of acute lupus erythematosus, Schaumann (17) found lesions in blood forming organs (lymph nodes, spleen and bone marrow), the histology of which he reported more or less typical of tuberculosis.

Ramel (18), though admitting that the histologic picture of lymph nodes in patients with lupus erythematosus was not that of tuberculosis, reported that by successive injection of lymph node and tissue from skin lesions of lupus erythematosus into guinea pigs, he was able eventually to obtain typical tuberculous lesions in these animals. The first series of animals to receive the injection of tissue from patients did not show the lesions of tuberculosis but by injecting emulsions of tissue from these animals into others, he was able to produce typical lesions of tuberculosis in the fourth or fifth animal passage. The same experiments were attempted by Olesoff and Reomenski (19) and Bohnstadt (20) but they obtained negative results. Ramel (21), using the same technic, reported similar findings with material obtained from patients who had erythema multiforme. His methods were repeated in this disease by Percival and Gibson (22) and by Hallam and Edington (23) with completely negative results. His method is reasonably criticized by the authors just mentioned. Cannon and Ornstein (24), following Ramel's suggestion, were able to produce tuberculosis in guinea pigs with the material from five patients out of twenty-three studied. On the other hand, there are numerous earlier reports of the failure of such investigations, for example those of Ehrmann and Falkenstein (25), Delbanco (26), Mebert (27), Verrotti (28), and Tyshnenko (29).

Kren and Lowenstein (30, 31, 32) and Lowenstein and Ruseff (33) reported that by the use of a special technic developed by Lowenstein positive blood cultures for tubercle bacilli could be obtained in a high percentage of patients who had lupus erythematosus (77 per cent). A group including Konrad (34), Fischer (35), Schwabacher (36), Lichtenstern (37), Mathiesen (38) and Ashimura (39) obtained results that were about 50 per cent positive by Lowenstein's method. Nanu, Janesco and Stefanesco (40), Popper *et al* (41) and Jontofsohn (42) were undecided as to the value of the method. Another group including Horster (43), Bingold, (44), Weber (45), Kallos (46), Matras (47), Grimm (48), Favero (49), Unverricht and S. Dosquet (50), Laymon (51) and others (52) (mentioned in the Berlin Dermatological Society) obtained few if any positive results.

Of interest is the report of Molesworth (53) (1933) who recorded the observation that in Australia, while lupus erythematosus is common, lupus vulgaris is almost unheard of as are also the tuberculids. In addition he noted that patients with lupus erythematosus came more often from the highlands and inland than from the coast where the incidence of tuberculosis was higher.

The statistics in this country agree with those reported by Molesworth, in that in the eastern states of America lupus vulgaris is frequent and tuberculosis is common; in the western states lupus vulgaris is rare unless imported from the eastern states and tuberculosis is less common but lupus erythematosus occurs as frequently in the western states as it does in the eastern or as it does in Europe where the incidence of tuberculosis is even higher (54).

A syphilitic background but not a direct syphilitic cause for lupus erythematosus is suggested by Gouin (55) *et al* on the basis of the fact that all except one of the cases which they studied showed a leukocytosis following antisyphilitic remedies, particularly bismuth.

Fullenbaum and Fleck (56) reported the results of intradermal tests in forty-three patients with lupus erythematosus using old tuberculin, Danysz vaccine (a polyvalent pyogenic-cocci vaccine) and Delbet vaccine (a polyvalent enteric vaccine). A positive focal reaction in the areas of lupus erythematosus was obtained in eleven of those forty-three patients with old tuberculin, in twenty-two with the Danysz vaccine and in eleven with the Delbet vaccine. These investigators performed complement fixation reactions with the serum from patients with lupus erythematosus using as antigens the Danysz and Delbet vaccines. They found striking agreement of the serologic and cutaneous tests.

Forman (57) tested twenty-one patients with lupus erythematosus with vaccine of Streptococcus hemolyticus, Streptococcus viridans and staphylococcus and old tuberculin. He used forty-one patients with psoriasis as controls. He obtained a high proportion of positive reactions to the hemolytic streptococcus, suggesting a specific sensitization to this organism. Streptococci have been reported in cultures of the blood before and after death by many authors in the acute form of the disease (Lyon (12), Madden (2), Roxburgh (6), Weidman and Gilman (13), O'Leary (8) and others). The cause of death in most patients with acute disseminate lupus erythematosus is streptococcal septicemia rather than tuberculosis in any of its forms. Prochazka (58) treated thirty-one cases of lupus erythematosus with hemolytic streptococcus vaccine; eight were cured and twelve improved.

From an analysis of the reviews of F. Veidel (1), Madden (2), and Mook, Weiss and Bromberg (3), and of the evidence just reviewed it is apparent that as yet no conclusive proof exists for any of the etiologic theories suggested for lupus erythematosus.

BACTERIOLOGIC STUDIES

This report deals with the bacteriologic studies of the blood, of material from the nasopharynx and of material from infected tonsils and the apices of infected teeth in sixteen patients who had disseminate lupus erythematosus. The cultural results obtained are recorded in table 1. A total of forty-three pure cultures of a characteristic streptococcus were isolated from the above sources from these patients. The technic employed in every procedure in these investigations on lupus erythematosus was identical in every detail to that already described as employed in similar studies on pemphigus (59, 60).

CHARACTERISTICS OF THE STREPTOCOCCUS

The morphologic, staining, cultural and fermentation characteristics of the streptococcus isolated from patients who had lupus erythematosus are similar and indistinguishable from these properties as described for the specific streptococcus isolated from patients with dermatitis herpetiformis (61).

Determinations of cataphoretic mobility.—The two peaks (1.72 and 3.45) in the cataphoretic mobility distribution curve (fig. 1) of streptococci which were isolated from the blood, the nasopharynges and foci of infection of patients with lupus erythematosus, as determined by means of the Mudd assembly of the

Northrop-Kunitz apparatus, were the same as those already described for the streptococcus from pemphigus (60), and for other streptococci having elective localizing properties for ectodermal tissues (62, 63, 64).

INJECTION INTO ANIMALS

The organism was injected into a total of 171 mice, rats, guinea pigs and rabbits. The freshly isolated organism was found to be virulent for animals of each of these four species. In contrast to the streptococcus isolated from patients who had pemphigus, this organism was not especially virulent for mice. The dead organism, when injected intravenously into rabbits in the manner described in similar studies with the streptococcus from dermatitis herpetiformis

TABLE 1

Cultural results obtained in sixteen patients who had disseminated lupus erythematosus

NUMBER OF	MATERIAL CULTURED			
	Swabbings from nasopharynx	Blood	Tonsils	Teeth
Patients from whom material was studied	16	10	2	1
Patients from whom characteristic streptococcus was recovered	16	6	2	1
Attempts to recover characteristic streptococcus	31	14	2	1
Attempts resulting in recovery of characteristic streptococcus	21	7	2	1
Pure cultures of characteristic streptococcus obtained	32	8	2	1

A total of forty-three pure cultures of a characteristic streptococcus were isolated from the above sources from these sixteen patients who had lupus erythematosus.

(61) produced hemorrhages in the skin in 74 per cent of the animals tested. No attempt was made to reproduce the clinical picture of lupus erythematosus in animals with this organism.

EXPERIMENTS TO ESTABLISH THE IDENTITY OF THE INDIVIDUAL STRAINS[2] OF THE STREPTOCOCCUS

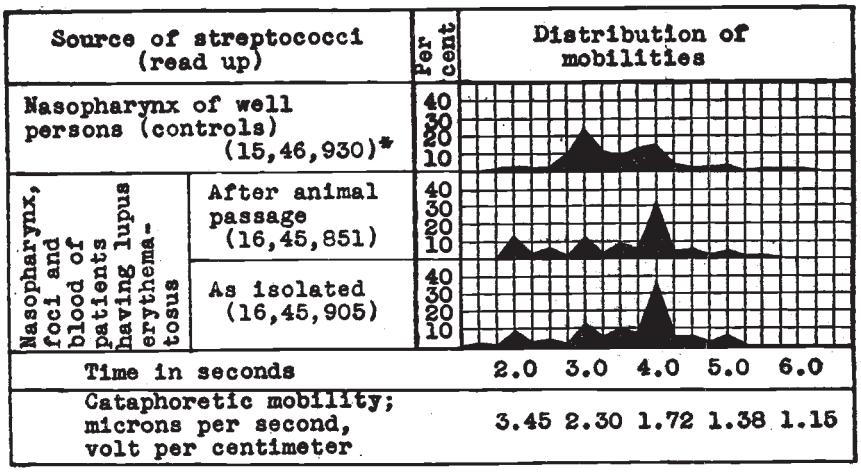
Agglutination reactions with immune horse and immune rabbit serums.—The titer of agglutinins in the serums of patients who had lupus erythematosus was found to be insufficient to demonstrate clearly cross agglutination of the different strains of the streptococcus isolated from patients with lupus erythematosus. Therefore each of ten rabbits was immunized with a single strain and a

[2] In order to avoid confusion, the word "strain" in the remainder of this paper is applied to each of the individual pure cultures of the organism isolated from patients who had lupus erythematosus. It is used in the same manner in referring to streptococci isolated from patients with other diseases.

horse (103) was immunized with a mixture of eight strains of this streptococcus.

As is indicated in table 2, each of the immune rabbit serums and the immune horse serum agglutinated to some degree all, and to a marked degree most, of the ten strains of the streptococcus from patients with lupus erythematosus (strains other than those strains used to immunize the animals) but failed to agglutinate the control streptococci from pemphigus, dermatitis herpetiformis and erythema multiforme, except in the few instances indicated in the table. A control pool of immune rabbit serums and an immune horse serum as well as normal rabbit and normal horse serum agglutinated a few of these strains slightly.

After demonstrating cross agglutination with each immune rabbit serum, a pool was made of equal quantities of the ten serums. This pool of immune



*The figures in parenthesis indicate respectively, the number of strains, cultures, and streptococci timed in each group.

FIG. 1. DISTRIBUTION CURVES OF THE CATAPHORETIC TIME AND MOBILITY OF STREPTOCOCCI ISOLATED FROM THE NASOPHARYNX, FOCI AND BLOOD OF PATIENTS SUFFERING FROM LUPUS ERYTHEMATOSUS DISSEMINATUS

rabbit serums and the serum from a horse (103) after immunization for more than a year, were used as agglutinating serums to test other individual heterologous strains isolated from patients with lupus erythematosus.

As is shown in table 3, the serum from horse 103 and the pool of immune rabbit serums described above agglutinated each of ten individual heterologous strains of streptococci from lupus erythematosus. It is also shown that the control immune serums from horses 99, 104 and 105 immunized (for more than one year) with streptococci from pemphigus, dermatitis herpetiformis and erythema multiforme respectively and control pooled serums from rabbits similarly immunized, agglutinated slightly two of these ten strains of streptococci from lupus erythematosus. One of these ten strains from lupus erythematosus was also agglutinated slightly in normal horse serum and in physiologic salt solution.

None of the control suspensions of streptococci from pemphigus, dermatitis herpetiformis and erythema multiforme was agglutinated by the serum from horse (103) or in the pool of serums from rabbits immunized with the streptococcus from lupus erythematosus, whereas each was agglutinated strongly in the serum from the horse and the pooled serums from rabbits which had been

TABLE 2

Agglutination reactions

Individual serums from ten rabbits immunized with single strains, and the serum of a horse immunized with a pool of eight strains of streptococci isolated from patients with lupus erythematosus, agglutinate ten strains of streptococci from other patients with the same disease.

STREPTOCOCCI FROM PATIENTS WITH:	STRAIN NUMBER	INDIVIDUAL SERUMS FROM RABBITS IMMUNIZED TO SINGLE STRAINS OF STREPTOCOCCI ISOLATED FROM PATIENTS WHO HAD LUPUS ERYTHEMATOSUS (DILUTION 1:20)										SERUM OF IMMUNE HORSE 103*	CONTROL SERUMS IMMUNIZED TO STREPTOCOCCI FROM PEMPHIGUS		(1:20) NORMAL		SALT SOLUTION
		Rabbit											Rabbit	Horse	Rabbit	Horse	
		454	456	457	458	459	461	462	464	466	467						
Lupus erythematous (single strains)	1	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	1+	−	−	−	−
	2	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	2+	1+	−	1+	−	−
	3	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	1+	1+	1+	1+	−
	4	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	3+	−	−	−	−	−
	5	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	−	−	−	−	−
	6	3+	2+	1+	3+	3+	1+	3+	4+	1+	4+	2+	−	−	−	−	−
	7	4+	3+	4+	2+	3+	2+	4+	3+	3+	3+	3+	−	−	−	−	−
	8	4+	2+	3+	3+	2+	1+	2+	1+	4+	4+	2+	−	−	−	−	−
	9	2+	4+	4+	4+	2+	1+	1+	1+	2+	1+	4+	−	−	−	−	−
	10	2+	2+	3+	2+	1+	3+	1+	2+	2+	3+	4+	1+	−	−	−	−
Pemphigus (pool of 19 strains)		−	−	−	−	−	−	−	−	−	−	−	2+	4+	−	−	−
Dermatitis herpetiformis (pool of nine strains)		−	−	−	−	−	−	−	1+	1+	1+	−	−	−	−	−	−
Erythema multiforme (pool of 7 strains)		−	−	−	−	−	1+	1+	−	−	−	−	−	−	−	−	−

* This horse was immunized with pool of eight strains of streptococci isolated from patients who had lupus erythematosus.

immunized with streptococci from patients with the respective disease. Fifteen other single heterologous strains of streptococci isolated from lupus erythematosus gave approximately the same results as the ten recorded in this table. These results suggest that the different strains of the streptococcus tested are identical in type.

It is apparent after consideration of the results recorded in tables 2 and 3 that

enough similarity exists between streptococci from patients with lupus erythematosus, pemphigus, dermatitis herpetiformis and erythema multiforme to produce some cross agglutination in the serums from animals which were immunized for extended intervals with these individual organisms.

Agglutinin-absorption in pooled immune rabbit and immune horse serums.—It

TABLE 3

Agglutination reactions between single strains of the streptococcus isolated from patients who had lupus erythematosus and pooled immune rabbit serums and immune horse serums

STREPTOCOCCI FROM PATIENTS WITH:	STRAIN NUMBER	HORSE SERUM (1:2000)					POOLED RABBIT SERUM (1:200)					
		Horse 103 immunized with eight strains from lupus erythematosus	Horse 99 immunized with nineteen strains from pemphigus	Horse 104 immunized with nine strains from dermatitis herpetiformis	Horse 105 immunized with seven strains from erythema multiforme	Normal	Immunized with eight strains from lupus erythematosus	Immunized with seven strains from pemphigus	Immunized with seven strains from dermatitis herpetiformis	Immunized with five strains from erythema multiforme	Normal	Salt Solution control
Lupus erythematosus (single strains)	11	3+	–	–	–	–	3+	–	–	–	–	–
	12	4+	–	–	–	–	3+	–	–	–	–	–
	13	4+	1+	1+	1+	1+	4+	–	1+	1+	–	1+
	14	3+	–	–	–	–	2+	–	–	–	–	–
	15	2+	–	–	–	–	1+	–	–	–	–	–
	16	2+	–	–	–	–	3+	–	–	–	–	–
	17	4+	–	–	–	–	4+	–	–	–	–	–
	18	3+	–	–	–	–	3+	–	–	–	–	–
	19	4+	–	–	–	–	4+	–	–	1+	–	–
	20	3+	–	–	–	–	3+	–	–	–	–	–
Pemphigus (pool of 19 strains)		–	4+	–	–	–	–	4+	–	–	–	–
Dermatitis herpetiformis (pool of 9 strains)		–	–	4+	–	–	–	–	4+	–	–	–
Erythema multiforme (pool of 7 strains)		–	–	–	4+	–	–	–	–	4+	–	–

* Fifteen other single heterologous strains isolated from patients who had lupus erythematosus gave approximately the same results as the ten recorded above.

is shown in table 4 that by the absorption of the pool of immune rabbit serums with each of six single strains and, in table 5, that by absorption of the immune horse serum with each of ten heterologous strains of streptococci from lupus erythematosus the agglutinins for twenty strains, which were shown to be agglutinated by these untreated serums, were removed by them.

Absorption of this pool of immune rabbit serums with control strains of strepto-

cocci from pemphigus and arthritis, and absorption of the immune horse serum with control streptococci from dermatitis herpetiformis failed to show removal from these serums of the agglutinins for any of the twenty strains of streptococci from lupus erythematosus; the pool of immune rabbit serums and the immune horse serum thus treated acted exactly as did these serums untreated.

TABLE 4

Agglutinin-absorption reactions

Absorption from pooled immune rabbit serums of agglutinins for twenty strains of streptococci isolated from patients who had lupus erythematosus by single strains of streptococci from patients with the same disease.

STREPTOCOCCI FROM PATIENTS WITH:	STRAIN NUMBER	NORMAL RABBIT SERUM	POOLED IMMUNE RABBIT SERUMS (1:200)									SALT SOLUTION CONTROL
				Treated with streptococci from patients with:								
			Untreated	Lupus erythematosus (strain 5)	Lupus erythematosus (strain 6)	Lupus erythematosus (strain 8)	Lupus erythematosus (strain 9)	Lupus erythematosus (strain 14)	Lupus erythematosus (strain 17)	Pemphigus (pool of nineteen strains) #102	Arthritis (pool of six strains) #5418	
Lupus erythematosus (single strains)	1	—	4+	—	—	—	—	—	—	4+	4+	—
	2	—	4+	—	—	—	—	—	—	3+	3+	—
	4	—	4+	—	—	—	—	—	—	4+	4+	—
	5	—	4+	—	—	—	—	—	—	3+	3+	—
	6	—	3+	—	—	—	—	—	—	3+	3+	—
	7	—	3+	—	—	—	—	—	—	3+	3+	—
	8	—	3+	—	—	—	—	—	—	2+	3+	—
	9	—	3+	—	—	—	—	—	—	3+	2+	—
	10	—	3+	—	—	—	—	—	—	2+	3+	—
	11	—	3+	—	—	—	—	—	—	2+	2+	—
	14	—	3+	—	—	—	—	—	—	3+	3+	—
	15	—	2+	—	—	—	—	—	—	2+	2+	—
	17	—	4+	—	—	—	—	—	—	4+	4+	—
	18	—	3+	—	—	—	—	—	—	3+	3+	—
	19	—	4+	—	—	—	—	—	—	3+	3+	—
	20	—	4+	—	—	—	—	—	—	4+	4+	—
	21	—	4+	—	—	—	—	—	—	3+	4+	—
	22	—	4+	—	—	—	—	—	—	4+	4+	—
	23	—	4+	—	—	—	—	—	—	2+	3+	—
	24	—	4+	—	—	—	—	—	—	3+	4+	—
Arthritis (pool of 6 strains #5418)		—	—	—	—	—	—	—	—	—	—	—

Precipitin reactions between immune horse serum and alkaline-saline extracts of the streptococcus.—Tests for precipitin reactions between the undiluted serum from immune horse (103) and alkaline-saline extracts of each of ten individual heterologous strains of the streptococcus from patients with lupus erythematosus were done.

Each of the ten undiluted extracts tested gave strong precipitin reactions (4+ according to the Rosenow scale (65)) with the undiluted serum from the horse which had been immunized with other strains of streptococci from patients with lupus erythematosus. Negative tests were obtained with the serum from a normal horse and with the serum from a horse which had been immunized with

TABLE 5

Agglutinin-absorption reactions

Absorption from immune horse serum of agglutinins for twenty strains of streptococci isolated from patients who had lupus erythematosus by single heterologous strains of streptococci from patients with the same disease.

STREPTOCOCCI FROM PATIENTS WITH:	STRAIN NUMBER	NORMAL HORSE SERUM	SERUM OF HORSE #103 IMMUNIZED WITH EIGHT STRAINS FROM LUPUS ERYTHEMATOSUS (DILUTION 1:2000)												SALT SOLUTION
				Treated with streptococci from patients with:											
			Untreated	Lupus erythematosus (strain 5)	Lupus erythematosus (strain 6)	Lupus erythematosus (strain 7)	Lupus erythematosus (strain 8)	Lupus erythematosus (strain 9)	Lupus erythematosus (strain 10)	Lupus erythematosus (strain 11)	Lupus erythematosus (strain 12)	Lupus erythematosus (strain 15)	Lupus erythematosus (strain 16)	Dermatitis herpetiformis (pool of nine strains #103)	
Lupus erythematosus (single strains)	1	–	4+	–	–	–	–	–	–	–	–	–	–	4+	–
	2	–	2+	–	–	–	–	–	–	–	–	–	–	2+	–
	4	–	3+	–	–	–	–	–	–	–	–	–	–	2+	–
	5	–	4+	–	–	–	–	–	–	–	–	–	–	3+	–
	6	–	3+	–	–	–	–	–	–	–	–	–	–	2+	–
	7	–	2+	–	–	–	–	–	–	–	–	–	–	2+	–
	8	–	3+	–	–	–	–	–	–	–	–	–	–	2+	–
	9	–	2+	–	–	–	–	–	–	–	–	–	–	2+	–
	10	–	3+	–	–	–	–	–	–	–	–	–	–	3+	–
	11	–	3+	–	–	–	–	–	–	–	–	–	–	2+	–
	14	–	3+	–	–	–	–	–	–	–	–	–	–	2+	–
	15	–	2+	–	–	–	–	–	–	–	–	–	–	2+	–
	17	–	4+	–	–	–	–	–	–	–	–	–	–	3+	–
	18	–	3+	–	–	–	–	–	–	–	–	–	–	3+	–
	19	–	4+	–	–	–	–	–	–	–	–	–	–	4+	–
	20	–	3+	–	–	–	–	–	–	–	–	–	–	3+	–
	21	–	4+	–	–	–	–	–	–	–	–	–	–	4+	–
	22	–	3+	–	–	–	–	–	–	–	–	–	–	3+	–
	23	–	4+	–	–	–	–	–	–	–	–	–	–	4+	–
	24	–	3+	–	–	–	–	–	–	–	–	–	–	2+	–
Arthritis (pool of six strains #5418)		–	–	–	–	–	–	–	–	–	–	–	–	–	–

streptococci from patients who had arthritis. Control tests with the serums from three other horses immunized individually with streptococci from patients with pemphigus, dermatitis herpetiformis and erythema multiforme also gave some positive reactions with the above extracts. These reactions, however, were weaker and were graded 1+ to 2+.

Further tests between each of these ten undiluted extracts and the above immune serums (except the anti-arthritis serum) and euglobulin solutions of equal concentration from these serums were done, titrating the whole serums and the euglobulin solutions. Positive reactions were obtained between each of the extracts and the whole serum from the horse which had been immunized with streptococci from lupus erythematosus in dilutions of 1:1,000 to 1:5,000 and with the euglobulin solution from this serum in dilutions 1:100 to 1:500. Positive reactions were obtained with the control, whole immune serums only in dilutions of from 1:10 to 1:100 and with the euglobulin solutions from these control serums only when these solutions were undiluted or diluted 1:5.

From these results it is apparent that the precipitinogen in alkaline-saline extracts of each of ten individual heterologous strains of streptococci from lupus erythematosus was strongly precipitated by the precipitins in the serum from a horse immunized with other heterologous strains of streptococci from the same source. These results suggest that the precipitinogens in each of the ten extracts are identical and constitute presumptive evidence that the different strains of streptococci from which these extracts were obtained are identical in type.

The weak cross precipitin reactions obtained between these extracts and the control immune serums suggest that the streptococci from the three control diseases are related to but distinct from the streptococcus from lupus erythematosus. Further control tests between these alkaline-saline extracts and the serum from a horse which had been immunized with streptococci from arthritis and the serum from a normal horse gave entirely negative results.

Precipitin reactions between immune horse serums and the specific soluble polysaccharide substance of the streptococcus.—Tests for precipitin reactions between the undiluted immune horse serums described above and the specific soluble polysaccharide substance (hereafter abbreviated to S.S.P.) prepared from each of ten individual heterologous strains of streptococci from patients with lupus erythematosus were performed. Each of the ten S.S.P.'s obtained, in a concentration of 1:5,000 in 0.9 per cent solution of sodium chloride, gave strong precipitin reactions (4+) with the undiluted serum from the horse which had been immunized with streptococci from patients with lupus erythematosus. Negative tests were obtaind between these S.S.P.'s and the serum from a horse which had been immunized with streptococci from arthritis and with the serum from a normal horse. Other control tests with the serum from each of three horses which had been immunized with streptococci from pemphigus, dermatitis herpetiformis and erythema multiforme respectively, gave positive reactions with some of the above S.S.P.'s. These reactions were weaker and were graded 1+ to 2+.

Further precipitin tests were done, employing the following procedures: 1) testing the undiluted immune horse serums against each of the ten S.S.P.'s diluted in salt solution up to 1:500,000 and 2) testing the ten S.S.P.'s in concentration of 1:5,000 against the immune horse serums diluted up to 1:50,000. In 1), positive tests were obtained with the undiluted serum from the horse which had been immunized with streptococci from lupus erythematosus and each

of the S.S.P.'s in concentrations varying from 1:50,000 to 1:100,000, and in 2), positive tests were obtained between each of the S.S.P.'s (1:5,000) and the serum from this horse diluted 1:1,000 to 1:10,000. In 1), control tests were positive with the undiluted serums from each of three other horses immunized individually with streptococci from pemphigus, dermatitis herpetiformis and erythema multiforme and these S.S.P.'s in dilutions of 1:5,000 to 1:10,000 and in 2) positive tests were obtained between each of the S.S.P.'s (1:5,000) and these three control serums diluted 1:10 to 1:100.

Solutions of euglobulin of equal concentrations were prepared from each of these four immune serums. Precipitin reactions were done between each of the ten S.S.P.'s at a concentration of 1:5,000 and these euglobulin solutions undiluted and diluted 1:10, 1:50, 1:100, 1:500, 1:1,000, 1:3,000, and 1:5,000. Positive reactions were obtained between each of the S.S.P.'s and the euglobulin solution from the serum from the horse which had been immunized with streptococci from lupus erythematosus in dilutions of 1:1,000 to 1:3,000. The control euglobulin solutions prepared from the other three immune horse serums gave positive reactions with these S.S.P.'s only when undiluted or when diluted 1:10 to 1:50.

From these results it is apparent that the S.S.P.'s obtained from each of ten individual heterologous strains of streptococci from lupus erythematosus was precipitated by the serum from a horse which had been immunized with other heterologous strains of streptococci from the same source. This suggests that the S.S.P. from each of the ten strains of streptococci is identical and, therefore, that the different strains of streptococci from which these ten S.S.P.'s were obtained are identical in type. It is also apparent that the S.S.P. from each of these ten strains from lupus erythematosus was precipitated but to a much lesser degree by the serums from three horses immunized individually with streptococci from pemphigus, dermatitis herpetiformis and erythema multiforme. The cross precipitin reactions with the above immune serums suggest that the S.S.P. obtained from streptococci from lupus erythematosus is distinct from but related to the S.S.P. in streptococci from patients with the other three diseases named.

Reduction of the cataphoretic mobility of the streptococcus by immune animal serum.—The serums from two rabbits, each immunized with a single strain, and the serum from a horse immunized with a mixture of eight strains of streptococci from lupus erythematosus were shown individually to reduce the mobility of ten heterologous strains of streptococci from patients with the same disease, as compared with their mobility in a solution of sodium chloride, while these same serums reduced the mobility of control streptococci from pemphigus, dermatitis herpetiformis and erythema multiforme little or no more than did normal serums. The results of these tests parallel exactly those already described in similar tests in the study on pemphigus (60). It is unnecessary to repeat the details here.

Cataphoregic mobility in immune serums from which antibodies had been absorbed. It was also demonstrated that the mobility reducing action of the immune horse serum on ten heterologous strains of streptococci from lupus erythematosus could be removed by absorption of the antibodies from this serum with other single

heterologous strains of the same streptococcus. The detailed figures on these experiments are again omitted because they parallel so closely those obtained and recorded in similar studies on pemphigus (60).

EXPERIMENTS TO ESTABLISH A SPECIFIC RELATIONSHIP BETWEEN PATIENTS WITH LUPUS ERYTHEMATOSUS AND THE STREPTOCOCCUS

Precipitin reactions between cleared nasopharyngeal washings from patients with lupus erythematosus and immune animal serums.—Tests for precipitin reaction between cleared nasopharyngeal washings from patients with lupus erythematosus and the immune horse and pooled immune rabbit serums were performed. As is shown in table 6, positive reactions were obtained in sixty-seven or 81.8 per

TABLE 6

Positive precipitin reactions between cleared nasopharyngeal washings and serums of the horses immunized with the streptococcus from (1) patients who had lupus erythematosus and (2) patients with five other diseases

NASOPHARYNGEAL WASHINGS FROM PATIENTS WITH:	CASES	TESTS	INCIDENCE OF POSITIVE REACTIONS IN SERUMS FROM HORSES IMMUNIZED WITH STREPTOCOCCI FROM PATIENTS WITH:						NORMAL HORSE SERUM
			Lupus erythematosus (horse #103)	Pemphigus (horse #99)	Dermatitis herpetiformis (horse #104)	Erythema multiforme (horse #105)	Encephalitis (horse #96)	Arthritis (horse #94)	
Lupus erythematosus.....	16	82	67 (81.8%)	29 (35.3%)	26 (31.7%)	28 (34.1%)	9 (10.9%)	5 (6%)	0
Other skin diseases (herpes zoster, pityriasis rosea, lichen planus, etc.).....	23	23	1 (4.3%)	0	0	1 (4.3%)	4 (17.3%)	2 (8.7%)	0

cent of the eighty-two tests made with the serum from the horse which had been immunized with streptococci from lupus erythematosus. These same washings, when tested with control serums from horses (99), (104), and (105) which had been immunized with streptococci from pemphigus, dermatitis herpetiformis and erythema multiforme respectively, gave positive precipitin reactions in twenty-nine (35.3 per cent), twenty-six (31.7 per cent) and twenty-eight (34.1 per cent) respectively, of the eighty-two tests made. Other control tests with these same washings and the serums from other horses immunized with other types of streptococci gave positive precipitin reactions in a very small percentage of instances. These washings gave no reactions with normal horse serum. The serum from horse (103) which had been immunized with streptococci from lupus erythematosus gave positive reactions with only one (4.3 per cent) of the twenty-three tests

made with the cleared nasopharyngeal washings from patients with other skin diseases.

In table 7 it is shown that the results of precipitin reactions between the pooled serums from rabbits immunized with streptococci from lupus erythematosus, pemphigus, dermatitis herpetiformis and erythema multiforme and from a normal rabbit parallel closely those described above (and recorded in table 6) between these same washings and serums from horses immunized with the same streptococci.

The results of these tests indicate that the cleared nasopharyngeal washings from the patients with lupus erythematosus contain a precipitinogen which is precipitated in a high percentage of the tests made with the serum from a horse

TABLE 7

Precipitin reactions between cleared nasopharyngeal washings and pooled serums from rabbits immunized with streptococci from (1) patients who had lupus erythematosus and (2) patients who had three other diseases

NASOPHARYNGEAL WASHINGS FROM PATIENTS WITH:	CASES	TESTS	INCIDENCE OF POSITIVE REACTIONS IN POOLED SERUMS FROM RABBITS IMMUNIZED WITH STREPTOCOCCI FROM PATIENTS WITH:				NORMAL RABBIT SERUM
			Lupus erythematosus	Pemphigus	Dermatitis herpetiformis	Erythema multiforme	
Lupus erythematosus	18	64	50 (78.1%)	27 (42.1%)	22 (34.3%)	30 (46.8%)	1 (1.5%)
Other skin diseases (herpes zoster, pityriasis rosea, lichen planus, and so forth).....	20	20	0	1 (5%)	0	2 (10%)	1 (5%)

and with pooled serums from rabbits immunized with streptococci from other patients with lupus erythematosus.

Precipitin reactions between alkaline-saline extracts of the streptococcus and the serums from patients who had lupus erythematosus.—Tests for precipitin reactions between the alkaline-saline extracts of each of ten individual heterologous strains of streptococci from lupus erythematosus and twenty-five heterologous serums from patients with lupus erythematosus were performed. The bacterial extracts and serums were used undiluted. Of these tests 52.4 per cent were positive, (graded 3+ to 4+). Only 18.5 per cent of the control tests between each of these extracts and twenty serums from patients with pemphigus, dermatitis herpetiformis and erythema multiforme were positive (graded 1+ to 2+). None of the control tests between each of these extracts and five serums from normal persons were positive.

Precipitin reactions between the specific soluble polysaccharide substance of the streptococcus and the serums of patients with lupus erythematosus.—Tests for pre-

cipitin reactions between the S.S.P. (diluted 1:5,000) obtained from each of ten heterologous strains of streptococci from lupus erythematosus and twenty-five heterologous serums (used undiluted) from patients with lupus erythematosus were performed. Of these tests, 64.8 per cent were positive (graded 3+ to 4+). Only 17 per cent of control tests between each of these S.S.P.'s and twenty serums from patients with pemphigus, dermatitis herpetiformis and erythema

TABLE 8

Reduction of the average mobility of ten heterologous strains of streptococci isolated from patients who had lupus erythematosus by the serum of a patient who had lupus erythematosus

STREPTOCOCCI FROM PATIENTS WITH:	STRAIN NUMBER	AVERAGE MOBILITY IN NaCl (MICRONS PER SEC., VOLTS PER CM.)	AVERAGE REDUCED MOBILITY IN SERUMS FROM PATIENTS WITH: (MICRONS PER SECOND, VOLTS PER CM.) (DILUTION 1:320)				AVERAGE MOBILITY IN NORMAL HUMAN SERUM (MICRONS PER SEC., VOLTS PER CM.)
			Lupus erythematosus case #77	Pemphigus, case #75	Dermatitis herpetiformis, case #83	Erythema multiforme, case #66	
Lupus erythematosus (single strains)	1	1.74	0.74 (57%)	1.66 (5%)	1.69 (3%)	1.50 (14%)	1.87 (+7%)
	2	1.92	0.78 (59%)	1.52 (21%)	1.61 (16%)	1.47 (23%)	1.84 (4%)
	3	1.73	0.67 (61%)	1.51 (13%)	1.52 (12%)	1.47 (15%)	1.66 (4%)
	4	1.41	0.64 (55%)	1.70 (+21%)	1.68 (+19%)	1.57 (+11%)	1.74 (+23%)
	5	1.57	0.78 (50%)	1.65 (+6%)	1.61 (+3%)	1.55 (1%)	1.79 (+14%)
	6	1.57	0.75 (52%)	1.37 (13%)	1.48 (6%)	1.41 (10%)	1.85 (+18%)
	7	1.37	0.63 (54%)	1.76 (+28%)	1.73 (+26%)	1.72 (+26%)	1.89 (+38%)
	8	1.84	0.82 (55%)	1.45 (21%)	1.50 (18%)	1.52 (17%)	1.47 (20%)
	29	3.06	0.88 (71%)	2.35 (23%)	2.17 (29%)	2.26 (26%)	2.41 (21%)
	36	2.04	0.83 (54%)	1.85 (9%)	1.89 (7%)	1.91 (6%)	1.93 (5%)
Pemphigus (pool of eleven strains)		2.32	1.47 (36%)	0.89 (62%)	1.57 (32%)	1.46 (37%)	1.94 (16%)
Dermatitis herpetiformis (pool of two strains)		2.19	1.57 (28%)	1.74 (20%)	0.88 (60%)	1.62 (26%)	1.81 (17%)
Erythema multiforme (pool of 4 strains)		1.95	1.62 (16%)	1.65 (15%)	1.60 (17%)	0.97 (50%)	1.80 (7%)
Encephalitis (pool of 6 strains)		1.99	1.68 (16%)	1.71 (14%)	1.68 (16%)	1.75 (12%)	1.84 (8%)
Arthritis (pool of 6 strains)		2.02	2.00 (1%)	2.05 (+1%)	1.96 (3%)	1.91 (5%)	2.12 (5%)

* Figures in parentheses represent the average reduction of mobility, expressed in per cent, under the average mobility in the salt solution control.

multiforme were positive (usually graded 1+, occasionally 2+). None of the control tests between each of these S.S.P.'s and the serums from five normal persons was positive.

Reduction of the cataphoretic mobility of the streptococcus by serums from patients with lupus erythematosus.—The cataphoretic mobility of the streptococcus from patients with lupus erythematosus was determined in human serums. In table 8 it is shown that the serum of a patient with lupus erythematosus (case 77) markedly reduced the mobility of ten individual heterologous strains of

streptococci from patients with lupus erythematosus, as compared with their average mobility in a solution of sodium chloride. The control serums from three patients (cases 75, 83, and 66) reduced the mobility of these ten strains of streptococci from lupus erythematosus about equally and little more than did the serum from a normal person. Control streptococci from patients with five other diseases had their mobility reduced little or no more by the serum from (case 77) than by the serum from a normal person. It is apparent that the serums from

TABLE 9

Removal from serums from patients who had lupus erythematosus of the mobility reducing action on streptococci from lupus erythematosus by absorption with single heterologous strains of streptococci derived from patients with this disease

STREPTOCOCCI FROM PATIENTS WITH:	STRAIN NUMBER	AVERAGE MOBILITY IN NaCl (MICRONS PER SEC. VOLTS PER CM.)	AVERAGE MOBILITY IN SERUMS FROM PATIENTS WHO HAD LUPUS ERYTHEMATOSUS (DILUTION 1:320) (MICRONS PER SECOND, VOLTS PER CM.)						NORMAL SERUM
			Case no. 72			Case no. 77			
			Unabsorbed	Treated with streptococci from:		Unabsorbed	Treated with streptococci from:		
				Lupus erythematosus (strain 7)	Pemphigus (pool 102)		Lupus erythematosus (strain 5)	Dermatitis herpetiformis (pool 103)	
Lupus erythematosus (single strains)	2	1.91	0.85 (56%)*	1.85 (4%)	1.11 (43%)	0.78 (59%)	1.72 (10%)	1.07 (45%)	1.84 (4%)
	3	1.73	0.71 (59%)	1.81 (+5%)	1.03 (40%)	0.67 (61%)	1.49 (14%)	0.93 (46%)	1.66 (4%)
	4	1.41	0.77 (45%)	1.71 (+21%)	0.94 (34%)	0.64 (55%)	1.57 (+11%)	0.94 (34%)	1.74 (+23%)
Pemphigus (single strain)	12	2.46	1.74 (29%)	1.77 (28%)	1.75 (29%)	1.41 (37%)	1.79 (27%)	1.80 (27%)	1.99 (19%)
Dermatitis herpetiformis (single strain)	1	2.17	1.53 (29%)	1.86 (14%)	1.63 (25%)	1.50 (30%)	1.64 (24%)	1.55 (29%)	1.89 (13%)

* Figures in parentheses represent the average reduction of mobility, expressed in per cent, under the average mobility in the salt solution control.

the patients with pemphigus (case 75), dermatitis herpetiformis (case 83) and erythema multiforme (case 66) reduced to any great extent only the mobility of the streptococci isolated from patients with the respective disease. The serums from nine other patients who had lupus erythematosus gave results similar to those obtained in case (77) with the same antigens. The results of these tests may be interpreted as further evidence of the identity of the individual strains of streptococci from patients with lupus erythematosus.

Cataphoretic mobility in human serums from which antibodies had been ab-

sorbed.—In table 9 it can be seen that the serums from two patients with lupus erythematosus when absorbed with single heterologous strains of streptococci from lupus erythematosus reduced the mobility of the control and respective streptococci about equally. Each of these serums untreated and each treated with control streptococci markedly reduced the mobility of the respective streptococci and not that of the controls. Similar results were obtained by absorption of other serums from patients who had lupus erythematosus with still other individual heterologous strains of streptococci isolated from patients with that disease. The above-described phenomenon may also be interpreted as evidence

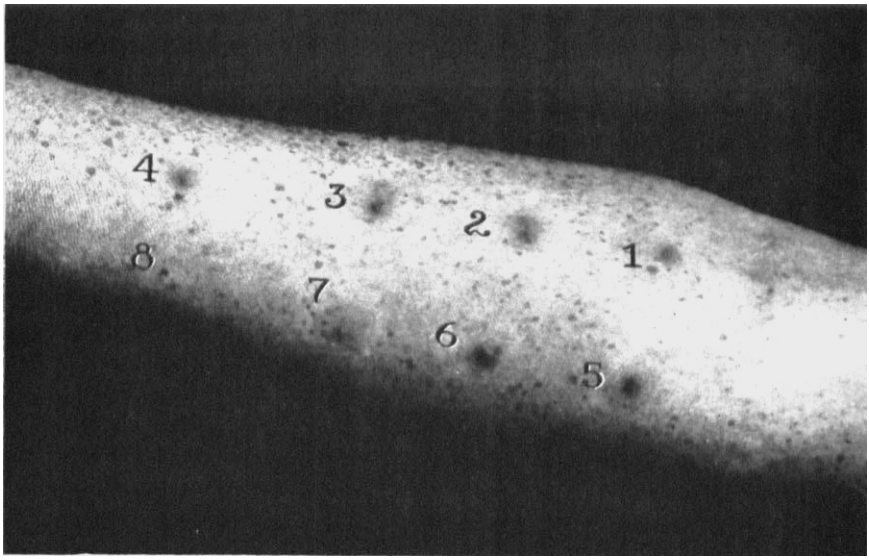


FIG. 2. LESIONS 1 TO 7 ARE ERYTHEMATOUS PAPULES PRODUCED BY INTRADERMAL INJECTION INTO A PATIENT WITH LUPUS ERYTHEMATOSUS OF INDIVIDUAL STRAINS OF THE SPECIFIC STREPTOCOCCUS

Number 8 is the site of a control injection of another streptococcus

of the identity of the individual strains of streptococci isolated from patients with lupus erythematosus.

Intradermal and subcutaneous injection of dead organisms into patients with lupus erythematosus.—Suspensions of streptococci, T 4,000, killed by heat, by formaldehyde solution or by hydrochloric acid were injected intradermally and subcutaneously into eleven patients with lupus erythematosus. An erythematous, indurated papule appeared in twenty-four hours at the site of each intradermal injection (fig. 2). Large doses of the dead streptococcus from lupus erythematosus when injected subcutaneously into five patients with lupus erythematosus produced extension of the disease process in the skin with additional areas of erythema in sites not previously involved.

Control intradermal injections of dead streptococci from patients with pemphigus, dermatitis herpetiformis and erythema multiforme and other cutaneous

and systemic diseases produced only areas of slight erythema at the point of injection in a few of these patients with lupus erythematosus. Intradermal injections of the dead streptococci from lupus erythematosus into patients with pemphigus, dermatitis herpetiformis and erythema multiforme produced, in some instances, small areas of erythema but never bullae.

Intradermal antiserum test.—Intradermal injections of whole serum from a horse which had been immunized with eight heterologous strains of streptococci from lupus erythematosus into six patients who had lupus erythematosus produced the characteristic erythema-edema (EE) reaction described by Foshay (66) in each patient tested. Control injections of the serums from a normal horse and from immune horses specific for other unrelated diseases produced no reaction in these same patients. Other control injections of the serums from three horses immunized individually with streptococci from pemphigus, dermatitis herpetiformis and erythema multiforme elicited an EE reaction in these patients who had lupus erythematosus but to only a very small fraction of the degree of reaction produced by the serum from the horse which had been immunized with streptococci from lupus erythematosus.

Solutions of equal concentration of the euglobulin fraction of the serums from five horses which had been immunized individually with streptococci from patients with lupus erythematosus, pemphigus, dermatitis herpetiformis, erythema multiforme and arthritis respectively, were prepared. These euglobulin solutions from the serums from the first four horses mentioned above elicited EE reactions in these patients with lupus erythematosus which paralleled exactly those described above for the whole serums from the same animals except that with these solutions the difference in degree of reaction between the specific and nonspecific serums was greater. Control intradermal injections of the whole serum and of the euglobulin fraction of the serum from the horse which had been immunized with streptococci from lupus erythematosus into normal persons and patients with unrelated cutaneous and systemic diseases elicited no reaction whatever. From these reactions it would seem that the streptococci from these four diseases are related but not identical in type. Foshay has pointed out that this reaction is a bacterial specific response and wholly unrelated to the phenomenon of serum protein sensitization and also that this reaction has been seen only when a patient with a given bacterial infection has been skin tested with antiserum specific for the infection.

SUMMARY

The morphologic, cultural, staining and fermentation characteristics of a streptococcus which has been isolated from patients with lupus erythematosus have been described. It has been shown to have a characteristic cataphoretic mobility distribution curve and has been found virulent for four species of animals. No attempt has been made to reproduce this disease in animals with this organism.

The different strains of this streptococcus have been shown to be serologically identical through the following procedures: 1) Agglutination reactions between

immune horse and immune rabbit serums and heterologous strains of the streptococcus, 2) reciprocal agglutinin-absorption reactions with heterologous strains of the streptococcus, 3) precipitin reactions between immune serums and alkaline-saline extracts of heterologous strains of the organism, 4) precipitin reactions between immune serums and the specific soluble polysaccharide substance of heterologous strains of the organism, 5) the cataphoretic mobility-reducing action of immune serums on heterologous strains of the organism, and 6) reciprocal absorption of the specific mobility-reducing action of immune serums.

A specific relationship between the patients with lupus erythematosus and this streptococcus has been demonstrated by the following methods: 1) precipitin reactions between the nasopharyngeal washings from patients with lupus erythematosus and the serums of animals immunized with the specific streptococcus, 2) precipitin reactions between alkaline-saline extracts of the organism and the serums from patients with lupus erythematosus, 3) precipitin reactions between the specific soluble polysaccharide substance of the streptococcus and the serums from patients with lupus erythematosus, 4) the cataphoretic mobility-reducing action of the serums from patients with lupus erythematosus on this streptococcus, 5) absorption by heterologous strains of the streptococcus of this specific mobility-reducing action from the serums from patients with lupus erythematosus, 6) the production of erythematous papules by intradermal and subcutaneous injection of the dead organism into patients with lupus erythematosus, 7) the production of the erythema-edema (EE) reaction of Foshay in patients with lupus erythematosus by the intradermal injection of immune horse serum.

It has also been shown that streptococci isolated from patients with pemphigus, dermatitis herpetiformis and erythema multiforme exudativum are similar but not identical in type to the streptococcus from patients with lupus erythematosus.

COMMENT

If the material presented here is to be accepted as factual, disseminate lupus erythematosus must be considered a streptococcal disease in which the streptococcus is present on the muccus membranes and in foci, from which repeated showers of organisms enter the blood stream. The lesions on the skin must be interpreted as the result of reaction in a sensitized individual to the organism itself or to the products of the growth of the organism in that person.

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